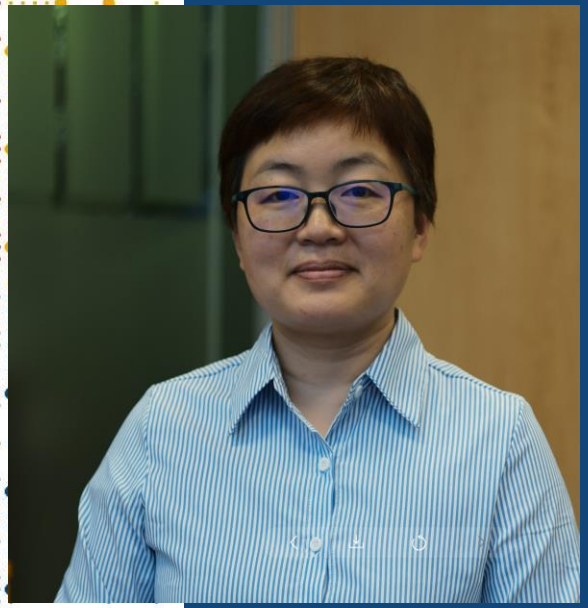
Understand PFDD Guidance Series and the Impact on Data Submission

Presented by Jintao Shi, Data Manager, Boehringer Ingelheim



Meet the Speaker

Jintao Shi

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Disclaimer and Disclosures

- *The views and opinions expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy or position of CDISC.*

- *The author(s) have no real or apparent conflicts of interest to report.*

Agenda

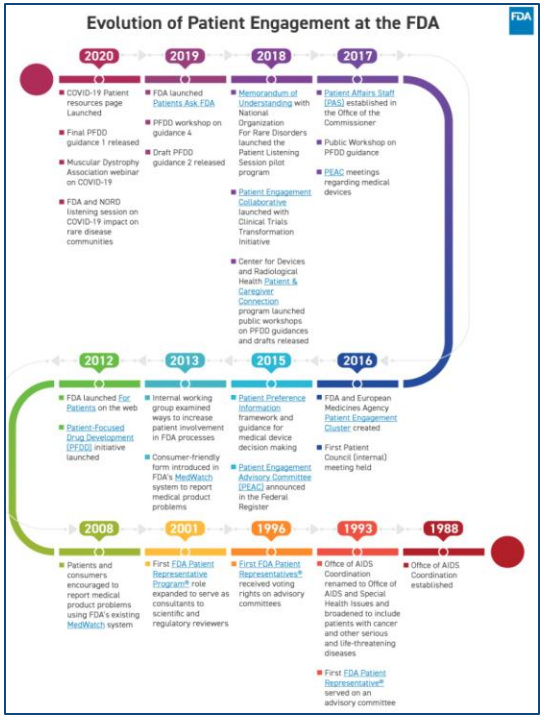
1. Increased Emphasis on Patient Voice
2. FDA PFDD Methodological Guidance Series
3. Guidance: Submitting PRO Data in Cancer Clinical Trials
4. Guidance: Submitting Clinical Trial Datasets & Documentation for COA Using IRT

Increased Emphasis on Patient Voice

Increased Emphasis on Patient Voice

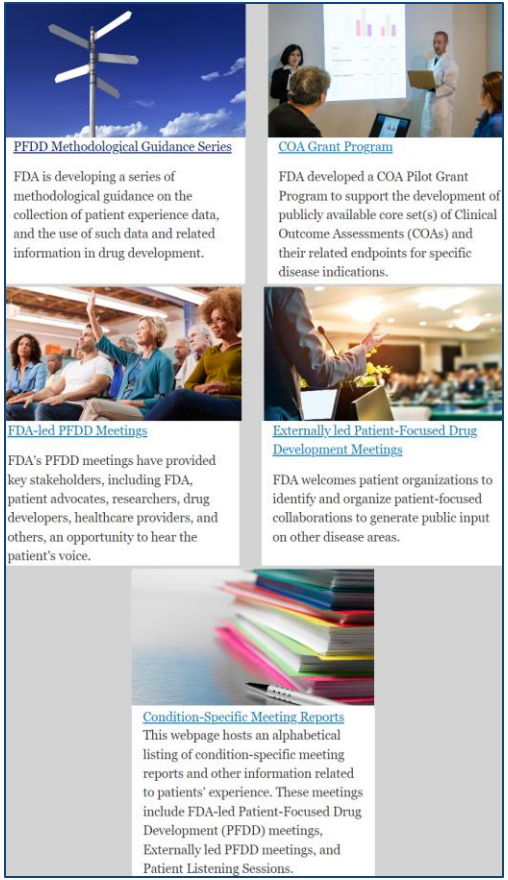
- Patients are the experts in the experience of their disease or condition, and they are the ultimate stakeholders in the outcome of medical treatment.
- Robust patient engagement approach is required to collect meaningful patient experience data and incorporate it in the whole drug developement lifecycle.
- Increased role and importance of patient experience data in all aspects of healthcare decision making, including drug development strategy from biopharmaceutical organizations, regulatory review and approval process from health authorities, and Health Technology Assessment (HTA) bodies assessment for pricing and reimbursement.

FDA U.S. FOOD & DRUG ADMINISTRATION



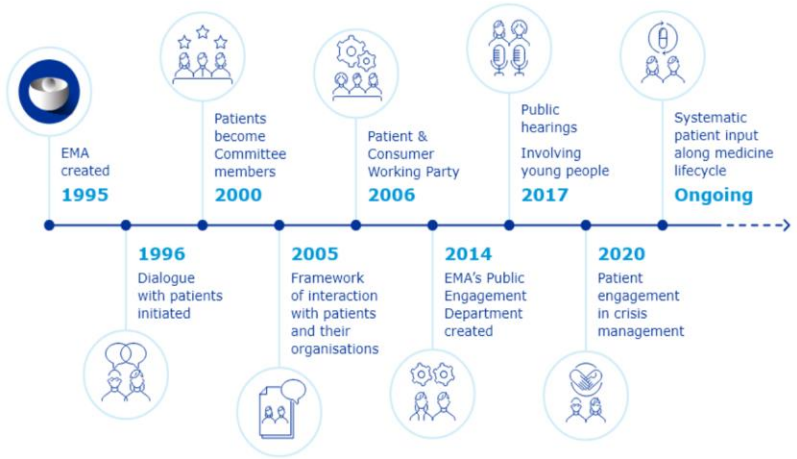
https://www.fda.gov/patients/evolution-patient-engagement-fda

https://www.fda.gov/drugs/development-approval-process-drugs/cder-patient-focused-drug-developmen



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Key milestones of EMA interaction with patients and consumers



https://www.ema.europa.eu/en/partners-networks/patients-consumers

Regulatory Science Strategy to 2025

On 31 March 2020, EMA published its Regulatory Science Strategy to 2025 after it was endorsed by EMA's Management Board at its March 2020 meeting.

EMA Regulatory Science to 2025 - Strategic reflection
Adopted
First published: 31/03/2020
Last updated: 31/03/2020

English (EN) (4.8 MB - PDF)

"Regulatory Science Strategy to 2025" proposes the core recommendation to "Ensure the patient voice is systematically incorporated throughout drug development & associated evidence generation"

Regulatory science strategy | European Medicines Agency (europa.eu)

独立行政法人 医薬品医療機器総合機構
Pharmaceuticals and Medical Devices Agency

Home > Regulatory Science/The Science Board/Standard Development > Regulatory Science > Projects Across Multi-Offices in PMDA > Patient Centricity WG

Regulatory Science/The Science Board/Standard Development

Patient Centricity WG

Document

- Pharmaceuticals and Medical Devices Agency Guidance on Patient Participation (September 7, 2021)

Past Presentations (Last 5 years)

- The outlook for Patient involvement in Medical Device Development ~Japanese Regulatory View~
  Japan-US HBD East 2021 Think Tank Meeting, Web, January 2022

- PMDA's Patient Participation Activities
  18th DIA Japan Annual Meeting 2021, Web, October 2021

Patient Centricity WG | Pharmaceuticals and Medical Devices Agency (pmda.go.jp)

NATIONAL MEDICAL PRODUCTS ADMINISTRATION
国家药品监督管理局

国家药品监督管理局药品审评中心
CENTER FOR DRUG EVALUATION, NMPA

当前位置：新闻中心>>工作动态>>通知公告>>新闻正文

国家药监局药审中心关于发布《以患者为中心的药物临床试验设计技术指导原则（试行）》《以患者为中心的药物临床试验实施技术指导原则（试行）》《以患者为中心的药物获益-风险评估技术指导原则（试行）》的通告（2023年第44号）

发布日期：20230727

“以患者为中心”的药物研发是指基于患者角度开展的药物开发、设计、实施和决策的过程，旨在高效研发更符合患者需求的有临床价值的药物，是当前各国药品监管机构积极探索的领域。为推动“以患者为中心”理念在药物研发的实践应用，药审中心组织制定了《以患者为中心的药物临床试验设计技术指导原则（试行）》《以患者为中心的药物临床试验实施技术指导原则（试行）》《以患者为中心的药物获益-风险评估技术指导原则（试行）》（见附件1—3）。根据《国家药监局综合司关于印发药品技术指导原则发布程序的通知》（药监综药管〔2020〕9号）要求，经国家药品监督管理局审查同意，现予发布，自发布之日起施行。

特此通告。

序号	
1	附件1.《以患者为中心的药物临床试验设计技术指导原则（试行）》.pdf
2	附件2.《以患者为中心的药物临床试验实施技术指导原则（试行）》.pdf
3	附件3.《以患者为中心的药物获益-风险评估技术指导原则（试行）》.pdf

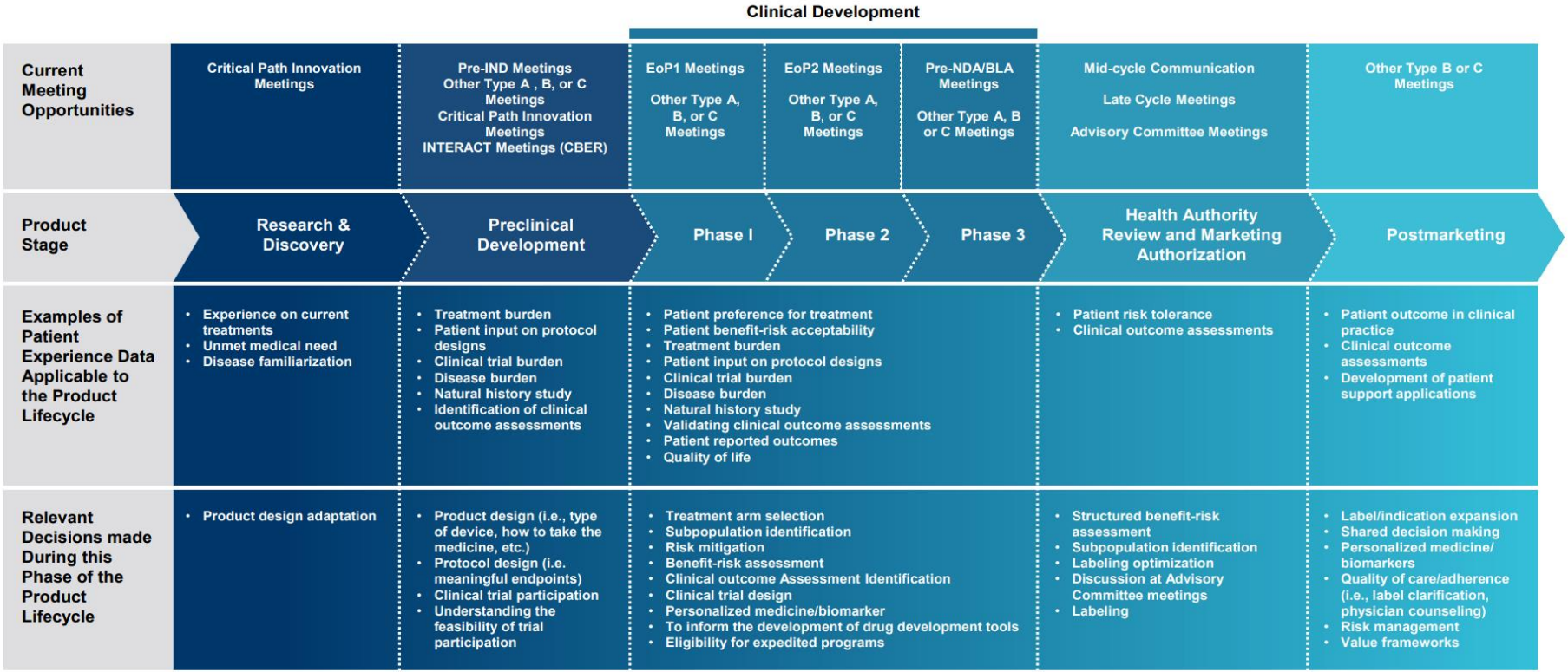
- Patient-centered study design
- Patient-centered study conduct
- Patient-centered risk-benefit assessment

https://www.cde.org.cn/main/news/viewInfoCommon/42c008e28f7004cd19b73949142380bd

BIO Framework for the Use of PED

Biotechnology Innovation Organization

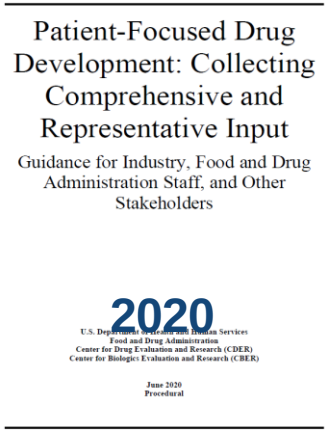
Framework for the Use of Patient Experience Data Throughout the Product Lifecycle

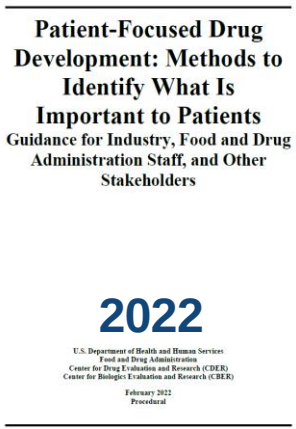


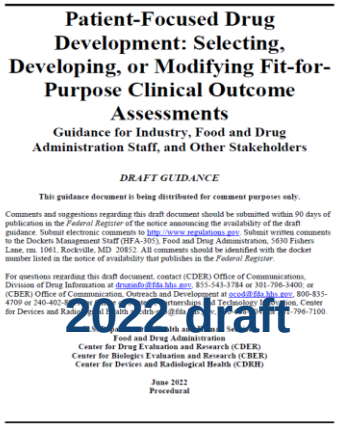
FDA PFDD Methodological Guidance Series

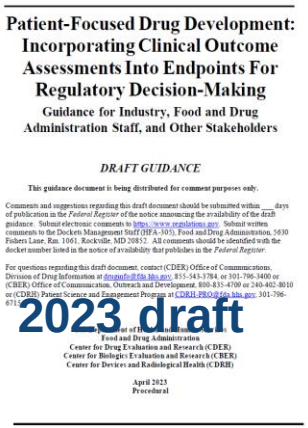
Background

- Patient Focused Drug Development (PFDD) is a systematic approach to help ensure that patients' experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into drug development and evaluation.
- Legislation is driving PFDD and increased, transparent use of Patient Experience Data in US.
  <2012 (Prescription Drug User Fee Act PDUFA V), 2017 (PDUFA VI), and 2022 (PDUFA VII), 2016 (21st Century Cures Act)>
- The series of PFDD guidance documents are part of FDA's efforts in accordance with the legislation requirements to facilitate the incorporation of patient experience data into medical product development.









C+TMF Interch

FDA PFDD Guidance

1. **Collecting Comprehensive and Representative Input**
   Overview of methods to collect robust, meaningful, and sufficiently representative patient input to inform medical product development and regulatory decision-making. Serve only as a basis for dialogue in the evolving and growing discipline of the science of patient input.

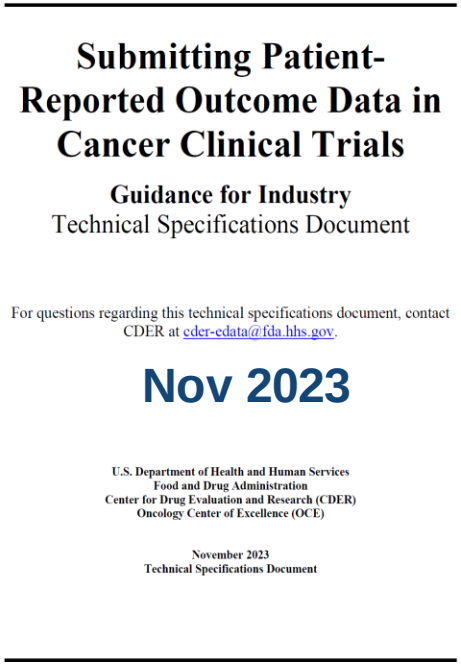
2. **Patient-Focused Drug Development: Methods to Identify What Is Important to Patients**
   Approaches to identifying what is most important to patients with respect to their experience as it relates to burden of disease/condition and burden of treatment

3. **Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments**
   Recommended approaches to selecting, modifying, developing, and validating fit-for-purpose clinical outcome assessments (COAs) to measure outcomes of importance to patients in clinical trials.

4. **Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments Into Endpoints For Regulatory Decision-Making**
   Methods, standards, and technologies for collecting and analyzing COA data for regulatory decision-making, including selecting the COA-based endpoint and determining clinically meaningful change in that endpoint.

Technical Specifications Guidance as Supplement

To supplement the PFDD Guidance Series, FDA issued two technical specifications guidance documents to provides specifications for submission of the standardized dataset content and structure of SDTM and ADaM datasets and specifications for recommended tables and figures.



Submitting Patient-Reported Outcome Data in Cancer Clinical Trials

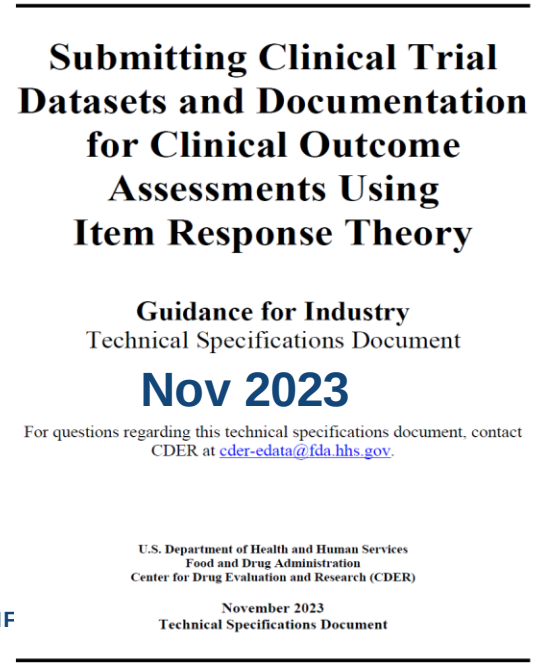
Guidance for Industry
Technical Specifications Document

For questions regarding this technical specifications document, contact CDER at cder-edata@fda.hhs.gov.

Nov 2023

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Oncology Center of Excellence (OCE)

November 2023
Technical Specifications Document



Submitting Clinical Trial Datasets and Documentation for Clinical Outcome Assessments Using Item Response Theory

Guidance for Industry
Technical Specifications Document

Nov 2023

For questions regarding this technical specifications document, contact CDER at cder-edata@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

November 2023
Technical Specifications Document

Guidance: Submitting PRO Data in Cancer Clinical Trials

SDTM *ADaM* *Tables&Figures*

SDTM

QS Domain

- Additional information to be considered in SUPPQS

SUPPQS Considerations	NSV for Reference
Data Collection Mode	ADMODP (Administration Mode of Presentation)
Language	DCLANG (Data Collection Language)
Data Collector	COLAID (Collected Administrator Identifier)
	COLRID (Collected Respondent Identifier)
	COLRRL (Collected Respondent Relationship)
	PPRAID (Preprinted Administrator Identifier)
	PPRRID (Preprinted Respondent Identifier)
	PPRRRI (Preprinted Respondent Relationship ID)
	…

Could be included in QX (or ZQ ?) domain which is under discussion by CDISC

- Missing data handling
  - -Different scenarios and suggested QSREASND terms.
  - -If PRO measurement is missed, normally each missing item and summary score shall be included
  - -Do not create data for unadministered items due to the use of computerized adaptive testing (CAT)

TS Domain

- TSPARAMCD = 'FDATCHSP'
- TSPARAM = 'FDA Tech Spec'
- TSVAL = 'Oncology PROs Technical Specifications Guidance v1.0'

ADaM

Possible match between SDTM.QS and ADQS

SDTM Variable	ADaM Variable
QSTESTCD	PARAMCD
QSTEST	PARAM
QSCAT	PARCAT1
QSSCAT	PARCAT2
QSSTRESN (quant.)	AVAL
QSSTRESC(qual.)	AVALC

- Following ADaM Basic Data Structure, support needs of analysis and keep traceability.
- Dataset name could be ADQS and use PARCAT1 to differentiate different instruments if multiple instruments exist.
- All individual item scores and summary scores shall be contained.

More scenarios of PARCATy usage

PARCAT1	PARCAT2	PARCAT3	PARCAT4	PARCAT5	PARAM
Measure Name and Version	ITEM	Subscale Score 1	Scale Score A	Scale Score B	Item 1
Measure Name and Version	ITEM	Subscale Score 1	Scale Score A	Scale Score B	Item 2
Measure Name and Version	ITEM	Subscale Score 1	Scale Score A	Scale Score B	Item 3
Measure Name and Version	ITEM	Subscale Score 2	Scale Score A	Scale Score B	Item 4
Measure Name and Version	ITEM	Subscale Score 2	Scale Score A	Scale Score B	Item 5
Measure Name and Version	ITEM	Subscale Score 3	Scale Score A	Scale Score B	Item 6
Measure Name and Version	SUBSCALE SCORE	Subscale Score 1	Scale Score A	Scale Score B	Subscale Score 1
Measure Name and Version	SUBSCALE SCORE	Subscale Score 2	Scale Score A	Scale Score B	Subscale Score 2
Measure Name and Version	SUBSCALE SCORE	Subscale Score 3	Scale Score A	Scale Score B	Subscale Score 3
Measure Name and Version	SCALE SCORE		Scale Score A	Scale Score B	Scale Score A
Measure Name and Version	SCALE SCORE		Scale Score A	Scale Score B	Scale Score B

PARCAT1	PARCAT2	PARCAT3	PARAM
	mptom 1	Attribute 1	Symptom 1 Attribute 1

ADaM (cont.)

Represent missing PRO Data

- Copying from the SDTM QS.QSSTAT = 'NOT DONE' and corresponding QS.QSREASND
- When not exist in SDTM QS dataset and required in ADQS, derive new phantom records with DTYPE = 'PHANTOM', QS.QSSTAT and QS.QSREASND both null, ADQS.AREASND could be derived for the reason not done if applicable.

PROEXPFL and PROSCMFL (Y or null)

PROEXPFL (PRO Expected Flag)	PROSCMFL(PRO Score Completed Flag)
• An indicator variable to specify whether the PRO parameter (e.g., the individual item or summary score reported within a row) corresponds to a planned (per protocol) PRO assessment timepoint. • If PRO objectives for both (1) clinical benefit and (2) safety and tolerability are present within the same trial, two PRO Expected Flag variables should be submitted within the ADQS dataset (e.g., PROEX1FL and PROEX2FL) with definitions for each variable provided within the study metadata.	• An indicator variable to specify whether the PRO item score or summary score is populated at a planned (per protocol) PRO assessment timepoint (i.e., where AVAL or AVALC is not empty/null).

ADaM (cont.)

Estimands Intercurrent Events handling in ADQS

Intercurrent Events: events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest. Intercurrent events should be addressed when describing the clinical question of interest to precisely define the treatment effect that is to be estimated.

PRO to Evaluate Clinical Benefit	PRO to Inform Safety and Tolerability
• ADQS records should be created for all randomized (including randomized but not treated) patients, even after intercurrent event (treatment discontinuation, death, etc.) if there is PRO measure originally planned. • Phantom records should be created if no records in SDTM.QS.	• ADQS records are mainly from period before treatment discontinuation. PRO measure after treatment discontinuation should be minimized to reduce patient burden. • It is not required to create Phantom records for assessment timepoints after a patient's death or for any timepoints for randomized but not treated patients.

ADaM (cont.)

Total Score calculated in ADQS only

AVALC is not included as standard results in quantitative

USUBJID	VISIT	AVISIT	PARCAT1	PARAM	PARAMCD	AVAL	QSSTAT	QSREASND	DTYPE	AREASND	DCTREAS	PROEXPFL	PROSCMFL	ONTRTFL
A_100_1	SCREENING	SCREENING	Measure Name and Version	I01-Item 1	I01	3						Y	Y	
A_100_1	SCREENING	SCREENING	Measure Name and Version	I01-Item 2	I02	5						Y	Y	
A_100_1	SCREENING	SCREENING	Measure Name and Version	Total Score	TS	8						Y	Y	
A_100_1	CYCLE 1 DAY 1	BASELINE	Measure Name and Version	I01-Item 1	I01		NOT DONE					Y		Y
A_100_1	CYCLE 1 DAY 1	BASELINE	Measure Name and Version	I01-Item 2	I02	4						Y	Y	Y
A_100_1	CYCLE 1 DAY 1	BASELINE	Measure Name and Version	Total Score	TS					NOT CALCULABLE		Y		Y
A_100_1	CYCLE 2 DAY 1	CYCLE 2 DAY 1	Measure Name and Version	I01-Item 1	I01	2						Y	Y	Y
A_100_1	CYCLE 2 DAY 1	CYCLE 2 DAY 1	Measure Name and Version	I01-Item 2	I02	4						Y	Y	Y
A_100_1	CYCLE 2 DAY 1	CYCLE 2 DAY 1	Measure Name and Version	Total Score	TS	6						Y	Y	Y
A_100_1	CYCLE 3 DAY 1	CYCLE 3 DAY 1	Measure Name and Version	I01-Item 1	I01		NOT DONE	PATIENT REFUSAL		PATIENT REFUSAL				
A_100_1	CYCLE 3 DAY 1	CYCLE 3 DAY 1	Measure Name and Version	I01-Item 2	I02		NOT DONE	PATIENT REFUSAL		PATIENT REFUSAL				
A_100_1	CYCLE 3 DAY 1	CYCLE 3 DAY 1	Measure Name and Version	Total Score	TS					PATIENT REFUSAL				
A_100_2	SCREENING	SCREENING	Measure Name and Version	I01-Item 1	I01	4								
A_100_2	SCREENING	SCREENING	Measure Name and Version	I01-Item 2	I02	5								
A_100_2	SCREENING	SCREENING	Measure Name and Version	Total Score	TS	9								
A_100_2	CYCLE 1 DAY 1	BASELINE	Measure Name and Version	I01-Item 1	I01		NOT DONE	HOSPITALIZATION		HOSPITALIZATION				
A_100_2	CYCLE 1 DAY 1	BASELINE	Measure Name and Version	I01-Item 2	I02		NOT DONE	HOSPITALIZATION		HOSPITALIZATION		Y		
A_100_2	CYCLE 1 DAY 1	BASELINE	Measure Name and Version	Total Score	TS					HOSPITALIZATION		Y		
A_100_2	CYCLE 2 DAY 1	CYCLE 2 DAY 1	Measure Name and Version	I01-Item 1	I01				PHANTOM	DEATH	DEATH			
A_100_2	CYCLE 2 DAY 1	CYCLE 2 DAY 1	Measure Name and Version	I01-Item 2	I02				PHANTOM	DEATH	DEATH			
A_100_2	CYCLE 2 DAY 1	CYCLE 2 DAY 1	Measure Name and Version	Total Score	TS				PHANTOM	DEATH	DEATH			
A_100_2	CYCLE 3 DAY 1	CYCLE 3 DAY 1	Measure Name and Version	I01-Item 1	I01				PHANTOM	DEATH	DEATH			
A_100_2	CYCLE 3 DAY 1	CYCLE 3 DAY 1	Measure Name and Version	I01-Item 2	I02				PHANTOM	DEATH	DEATH			
A_100_2	CYCLE 3 DAY 1	CYCLE 3 DAY 1	Measure Name and Version	Total Score	TS				PHANTOM	DEATH	DEATH			

Phantom records created for timepoint after patient death, AVAL, QSSTAT, QSREASND, PROEXPFL, PROSCMFL, and ONTRTFL are all null

PROEXPFL Considerations

- *Expected assessment timepoint per protocol, on therapy or at paused treatment (PROEXPFL=Y)*
- *Translation of the PRO measure is not available in the patient's language (PROEXPFL=null)*
- *PRO assessment timepoints after patient death (PROEXPFL=null)*
- *Patients who discontinued from treatment for reason other then death (PROEXPFL=Y for clinical benefit case. Measurement should be minimized after treatment discontinuation for safety/tolerability case)*
- *Patients who were randomized but not treated (PROEXPFL=Y for clinical benefit case, PROEXPFL=null for safety/tolerability case)*

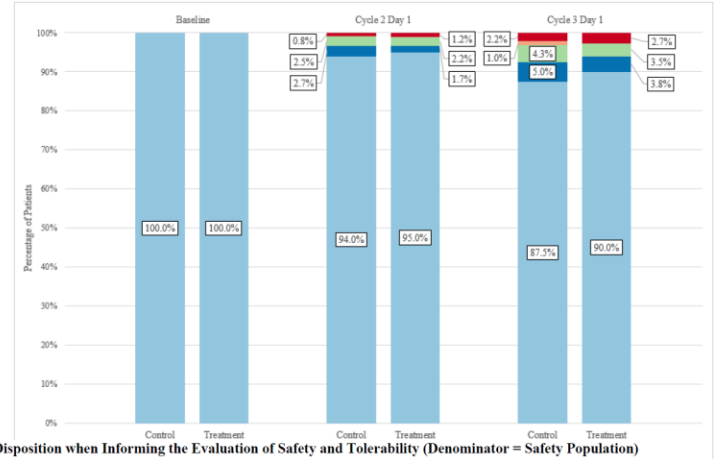
Table and Figures – patient disposition

Clinical benefit

Table A4. Patient Disposition when Evaluating Clinical Benefit (Denominator = Randomized Population)[1]

Analysis Visit	Treatment Arm	Randomized Patients (N)	PRO Expected[2]			
			Patients On Therapy, n (%)	Treatment Discontinuation: Disease Progression, n (%)	Treatment Discontinuation: Adverse Event (AE), n (%)	Treatment Discontinuation: Other Reasons, n (%)
Baseline	Control	600	600 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Treatment	602	602 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cycle 2 Day 1	Control	600	564 (94.0%)	16 (2.7%)	15 (2.5%)	0 (0.0%)
	Treatment	602	572 (95.0%)	10 (1.7%)	13 (2.2%)	0 (0.0%)
Cycle 3 Day 1	Control	600	525 (87.5%)	30 (5.0%)	26 (4.3%)	6 (1.0%)
	Treatment	602	542 (90.0%)	23 (3.8%)	21 (3.5%)	0 (0.0%)

Figure A1. Patient Disposition when Evaluating Clinical Benefit (Denominator = Randomized Population)



Safety and tolerability

Table A5. Patient Disposition when Informing the Evaluation of Safety and Tolerability (Deno

Analysis Visit	Treatment Arm	Randomized Population (N)	Safety Population (N)	PRO Expected,[5] n (%)	PRO Not	
					Death, n (%)	Treatment Discontinuation: Disease Progression, n (%)	Tr Disc A Ev
Baseline	Control	600	600	600 (100.0%)	0 (0.0%)	0 (0.0%)	0
	Treatment	602	602	602 (100.0%)	0 (0.0%)	0 (0.0%)	0
Cycle 2 Day 1	Control	600	600	564 (94.0%)	5 (0.8%)	16 (2.7%)	15
	Treatment	602	602	572 (95.0%)	7 (1.2%)	10 (1.7%)	13
Cycle 3 Day 1	Control	600	600	525 (87.5%)	13 (2.2%)	30 (5.0%)	26
	Treatment	602	602	542 (90.0%)	16 (2.7%)	23 (3.8%)	21

Figure A2. Patient Disposition when Informing the Evaluation of Safety and Tolerability (Denominator = Safety Population)

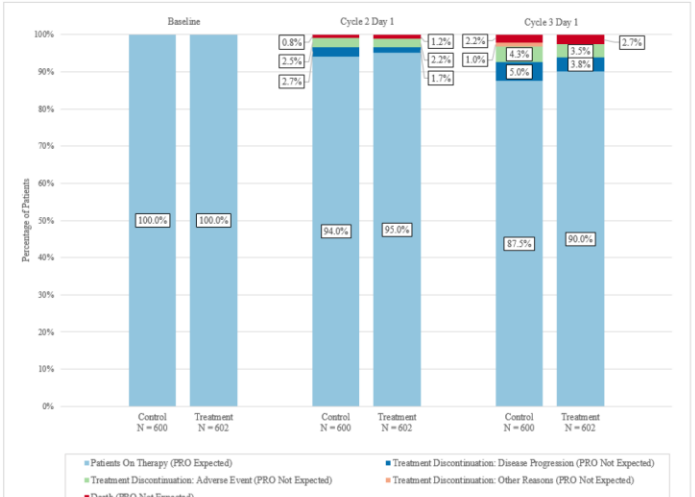


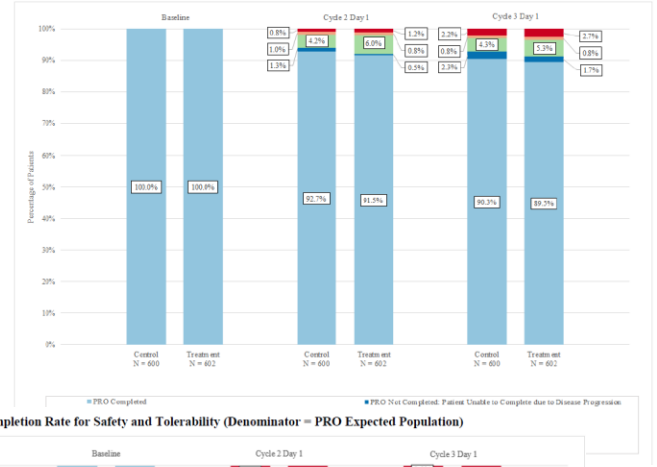
Table and Figures – available data rate & completion rate

Clinical benefit

Table A6. Available Data Rate for Clinical Benefit (Denominator = Randomized Population)[7]

Analysis Visit	Treatment Arm	Randomized Patients (N)	PRO Completed, n (%)	PRO Not Completed[8] (excluding Death), n (%)	Reason for PRO Not Completed,[9] n (%)				
					Patient Unable to Complete due to Disease Progression	Patient Unable to Complete due to Adverse Event (AE)	Patient Refusal	Device Failure	Reason Unknown,[10] n (%)
Baseline	Control	600	600 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Treatment	602	602 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cycle 2 Day 1	Control	600	556 (92.7%)	39 (6.5%)	8 (1.3%)	25 (4.2%)	6 (1.0%)	0 (0.0%)	0 (0.0%)
	Treatment	602	551 (91.5%)	44 (7.3%)	3 (0.5%)	36 (6.0%)	5 (0.8%)	0 (0.0%)	0 (0.0%)
Cycle 3 Day 1	Control	600	542 (90.3%)	45 (7.5%)	14 (2.3%)	26 (4.3%)	0 (0.0%)	5 (0.8%)	0 (0.0%)
	Treatment	602	539 (89.5%)	47 (7.8%)	10 (1.7%)	32 (5.3%)	5 (0.8%)	0 (0.0%)	0 (0.0%)

Figure A3. Available Data Rate for Clinical Benefit (Denominator = Randomized Population)



PROEXPFL = 'Y' and PROSCMFL="

Safety and tolerability

Table A7. Completion Rate for Safety and Tolerability (Denominator = PRO Expected Population)[11]

Analysis Visit	Treatment Arm	PRO Expected[12] (N)	PRO Completed, n (%)	PRO Not Completed, n (%)	Reason for PRO Not Completed,[13] n (%)			
					Patient Refusal	Patient Unable to Complete due to AE	Device Failure	Reason Unknown,[14] n (%)
Baseline	Control	600	600 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Treatment	602	602 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cycle 2 Day 1	Control	564	542 (96.1%)	22 (3.9%)	6 (1.1%)	16 (2.8%)	0 (0.0%)	0 (0.0%)
	Treatment	572	536 (93.7%)	36 (6.3%)	5 (0.9%)	31 (5.4%)	0 (0.0%)	0 (0.0%)
Cycle 3 Day 1	Control	525	510 (97.1%)	15 (2.9%)	0 (0.0%)	10 (1.9%)	5 (1.0%)	0 (0.0%)
	Treatment	542	516 (95.2%)	26 (4.8%)	5 (0.9%)	21 (3.9%)	0 (0.0%)	0 (0.0%)

Figure A4. Completion Rate for Safety and Tolerability (Denominator = PRO Expected Population)

Table and Figures – distribution

Table A8. Distribution of Categorical Responses for Item 1 (Safety and Tolerability Example)[15]

Analysis Visit	Treatment Arm	PRO Expected[16]	PRO Completed, n (%)	PRO Not Completed, n (%)	Response	
					Not at all	A litt
Baseline	Control	600	600 (100.0%)	0 (0.0%)	332 (55.3%)	220 (36.
	Treatment	602	602 (100.0%)	0 (0.0%)	313 (52.0%)	228 (37.
Cycle 2 Day 1	Control	564	542 (96.1%)	22 (3.9%)	299 (55.2%)	188 (34.
	Treatment	572	536 (93.7%)	36 (6.3%)	268 (50.0%)	199 (37.
Cycle 3 Day 1	Control	525	510 (97.1%)	15 (2.9%)	225 (44.1%)	189 (37.
	Treatment	542	516 (95.2%)	26 (4.8%)	203 (39.3%)	193 (37.

Table A9. Summary Statistics for Item 2 with Continuous Response Options (Safety and Tolerability Example)[18]

Analysis Visit		Control	Treatment
Baseline	PRO Expected[19] (N)	600	602
	PRO Not Completed, n (%)	0 (0.0%)	0 (0.0%)
	PRO Completed, n (%)	600 (100.0%)	602 (100.0%)
	Summary Statistics[20]		
	Mean	2.1	1.0
	Standard Deviation	1.8	0.9
	Standard Error	0.07	0.04
	Median	2.1	1.0
	Minimum	0.0	0.0
	Maximum	4.1	2.0
Cycle 2 Day 1	PRO Expected (N)	564	572
	PRO Not Completed, n (%)	22 (3.9%)	36 (6.3%)
	PRO Completed, n (%)	542 (96.1%)	536 (93.7%)
	Summary Statistics		
	Mean	7.1	5.1
	Standard Deviation	4.6	3.7
	Standard Error	0.19	0.15
	Median	7.2	5.1
	Minimum	0.3	0.2
	Maximum	11.8	9.8
Cycle 3 Day 1	PRO Expected (N)	525	542
	PRO Not Completed, n (%)	15 (2.9%)	26 (4.8%)
	PRO Completed, n (%)	510 (97.1%)	516 (95.2%)
	Summary Statistics		
	Mean	6.2	3.9
	Standard Deviation	5.2	2.7
	Standard Error	0.23	0.12
	Median	6.6	3.8
	Minimum	0.1	0.0

Figure A5. Distribution of Categorical Responses for Item 1 (Safety and Tolerability Example where Denominator = PRO Completed)

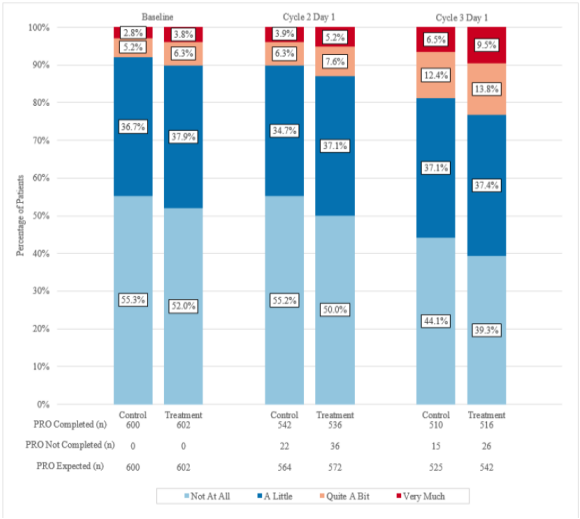


Figure A6. Descriptive Means for Item 2 with Continuous Response Options (Safety and Tolerability Example for Physical Functioning)[21,22]

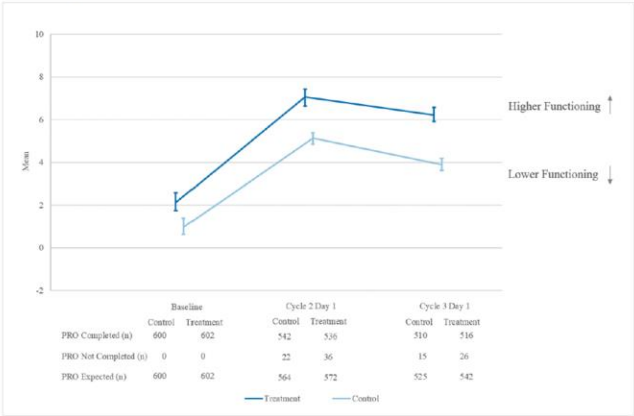


Table and Figures –distribution of change

Table A10. Distribution of Change in Response Categories from Baseline for Item 1 (Safety and Tolerability Exampl

Analysis Visit	Treatment Arm	PRO Expected[24]	PRO Completed, n (%)	PRO Not Completed, n (%)	Change in Response Categories,[25] n (%)					
					Improving 1	Improving 2	Improving 3	No Change	Worsening 1	Worsening 2
Cycle 2 Day 1	Control	564	542 (96.1%)	22 (3.9%)	38 (7.0%)	11 (2.0%)	3 (0.6%)	303 (55.9%)	132 (24.4%)	38 (7.0%)
	Treatment	572	536 (93.7%)	36 (6.3%)	33 (6.2%)	14 (2.6%)	6 (1.1%)	296 (55.2%)	141 (26.3%)	32 (6.0%)
Cycle 3 Day 1	Control	525	510 (97.1%)	15 (2.9%)	50 (9.8%)	24 (4.7%)	10 (2.0%)	261 (51.2%)	126 (24.7%)	29 (5.7%)
	Treatment	542	516 (95.2%)	26 (4.8%)	44 (8.5%)	28 (5.4%)	11 (2.1%)	261 (50.6%)	123 (23.8%)	39 (7.6%)

Table A11. Change from Baseline for Item 2 with Continuous Response Options (Safety and Tolerability Example)[26]

Analysis Visit		Treatment	Control
Cycle 2 Day 1	PRO Expected[27] (N)	564	572
	PRO Not Completed, n (%)	22 (3.9%)	36 (6.3%)
	PRO Completed, n (%)	542 (96.1%)	536 (93.7%)
	Summary Statistics[28]		
	Mean	4.9	4.5
	Standard Deviation	4.0	1.7
	Standard Error	0.17	0.19
	Median	5.0	4.2
	Minimum	-1.1	-1.3
	Maximum	10.3	9.0
Cycle 3 Day 1	PRO Expected[1] (N)	525	542
	PRO Not Completed, n (%)	15 (2.9%)	26 (4.8%)
	PRO Completed, n (%)	510 (97.1%)	516 (95.2%)
	Summary Statistics		
	Mean	4.1	2.9
	Standard Deviation	5.7	5.6
	Standard Error	0.25	0.24
	Median	4.2	2.9
	Minimum	-1.6	-1.4
	Maximum	8.0	8.5

Figure A7. Distribution of Change in Response Categories from Baseline for Item 1 (Safety and Tolerability Example where Denominator = PRO Completed)

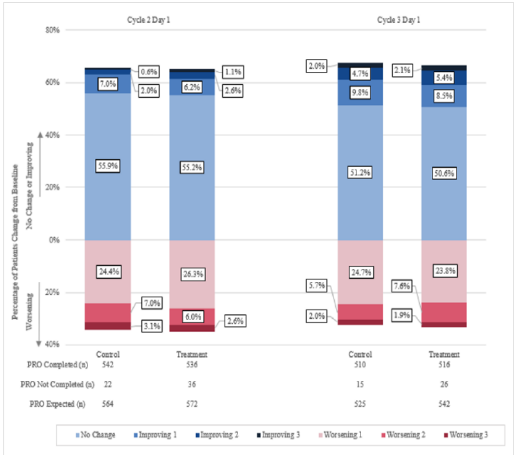


Figure A8. Change from Baseline for Item 2 with Continuous Response Options (Safety and Tolerability Example)[29 30]

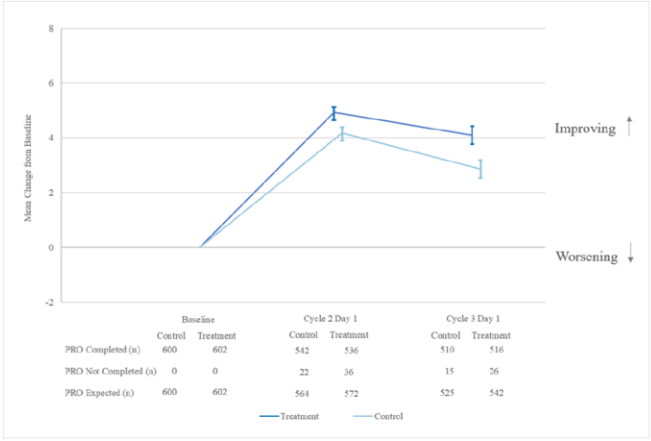


Table and Figures – healthcare utilization

5.3.7 *Incidence of Healthcare Utilization*

Table A12. Incidence of Healthcare Utilization (Safety and Tolerability Example where Denominator = PRO Expected)[31]

Analysis Visit	Treatment Arm	Randomized Patients	PRO Expected[32] (N)	Healthcare Utilization Intervention, n (%)					
				Emergency Department (ED) Visits	Hospitalizations	Opiates	Supportive Care Medications (e.g., Steroids, Transfusions, Growth Factors)	Supportive Care Procedures (e.g., Palliative: Hospice, Nephrostomy)	Other (Describe)
Baseline	Control	600	600	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Treatment	602	602	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cycle 2 Day 1	Control	600	564	5 (0.9%)	2 (0.4%)	0 (0.0%)	0 (0.0%)	3 (0.5%)	0 (0.0%)
	Treatment	602	572	5 (0.9%)	3 (0.5%)	0 (0.0%)	1 (0.2%)	1 (0.2%)	0 (0.0%)
Cycle 3 Day 1	Control	600	525	7 (1.3%)	5 (1.0%)	0 (0.0%)	0 (0.0%)	3 (0.6%)	0 (0.0%)
	Treatment	602	542	7 (1.3%)	3 (0.6%)	0 (0.0%)	2 (0.4%)	5 (0.9%)	0 (0.0%)

Guidance:Submitting Clinical Trial Datasets & Documentation for COA Using IRT

Item Response Theory (IRT)

IRT-based Computerized Adaptive Testing (CAT)

Scope and Background

- Fixed-form COAs that are developed and/or scored using Item Response Theory (IRT)
- COAs administered using IRT-based Computerized Adaptive Testing (CAT)

IRT	IRT-based CAT
Statistical framework used to model the relationship between latent traits (unobservable characteristics or attributes) and responses to items on a test or questionnaire. IRT can be used to develop, evaluate, and score COA measures. It provides a way to estimate the level of a latent trait based on a person's responses to a set of items. *Item parameters typically include:* • *Difficulty parameter: the level of the latent trait where a respondent has a 50% chance of endorsing the item (or in the case of polytomous models, of endorsing a particular response category or higher).* • *Discrimination parameter: how well the item differentiates between individuals at different levels of the latent trait.* • *Other: for example, item loading parameters for item with continuous response options*	*A sequential form of individual testing administered by a computer in which successive items in the COA measure are selected for administration based primarily on the item's psychometric properties and content in relation to the patient's responses to previous items, to provide individualized testing for a person.* *Selection is based on the likelihood that an item will be helpful in improving the estimate of the person's score, not on the relevance of the item content.*

Practical Guide to Conducting an Item Response Theory Analysis - Michael D. Toland, 2014 (sagepub.com)

Specific Information Required

When IRT is used for scoring

- Scoring details, including methods for generating scores (e.g., latent factor score (referred to as theta score throughout this document), scaled score)
- Conversion table(s) used to convert a theta score to other transformed scores (e.g., T-score), if applicable
- Psychometric software (e.g., the software name and version)

When COAs administered using CAT

- Details of item selection or routing algorithm (e.g., the algorithm used to select the next item or sets of items for the patient with content constraints and/or item exposure control (if applicable))
- The starting criteria with justification
- The termination criteria (i.e., the stopping rule) with justification

SDTM

Domain	Recommendations
ZQ - similar concept with QX domain which is under discussion by CDISC for SDTMIG 4.0	• Item dataset to represent for the item bank: all items, response options, and associated model parameters • when IRT is only used in scoring, the ZQ dataset should contain information for all items within the fixed/static COA • Domain for QRS reference, including RDOMAIN, both ZQTEST/CD and ZQPARM/CD, ZQVALN/C, and ZQSE(standard error)
QS, FT, RS	• --REFID could be used for covered COA measures that use CAT, since item selection and/or the order of item administration from the item bank can vary by patient and/or by assessment timepoint. • Recommended value for --REASND at different scenarios. • --ALL can be used as --TESTCD when COA measure using CAT and the measure is not administered. • Unadministered items due to the use of Computerized Adaptive Testing within the item bank should not be included within the QS dataset. • Additional variables in SUPP: Data Collection Mode, Data Collector, Language, Response Time
TS	• TSPARAMCD = 'FDATCHSP' • TSPARAM = 'FDA Tech Spec' • TSVAL = 'IRT-Based COAs Technical Specifications Guidance v1.0'

SDTM – ZQ example

All possible numeric and/or character response values for items, minimum/maximum and explanation

STUDYID	DOMAIN	RDOMAIN	ZQSEQ	ZQCAT	ZQTEST	ZQTESTCD	ZQPARMCD	ZQPARM	ZQVALN	ZQVALC	ZQSE
StudyA	ZQ	QS	1	Example Item Bank v.1.0	EIB01-Item 1	EIB01	RESP	Item Response	1	Never	
StudyA	ZQ	QS	2	Example Item Bank v.1.0	EIB01-Item 1	EIB01	RESP	Item Response	2	Rarely	
StudyA	ZQ	QS	3	Example Item Bank v.1.0	EIB01-Item 1	EIB01	RESP	Item Response	3	Sometimes	
StudyA	ZQ	QS	4	Example Item Bank v.1.0	EIB01-Item 1	EIB01	RESP	Item Response	4	Often	
StudyA	ZQ	QS	5	Example Item Bank v.1.0	EIB01-Item 1	EIB01	RESP	Item Response	5	Always	
StudyA	ZQ	QS	6	Example Item Bank v.1.0	EIB01-Item 1	EIB01	TPAR	Threshold Parameter	-1.2		0.29
StudyA	ZQ	QS	7	Example Item Bank v.1.0	EIB01-Item 1	EIB01	TPAR	Threshold Parameter	-0.6		0.14
StudyA	ZQ	QS	8	Example Item Bank v.1.0	EIB01-Item 1	EIB01	TPAR	Threshold Parameter	0.1		0.02
StudyA	ZQ	QS	9	Example Item Bank v.1.0	EIB01-Item 1	EIB01	TPAR	Threshold Parameter	0.8		0.13
StudyA	ZQ	QS	10	Example Item Bank v.1.0	EIB01-Item 1	EIB01	SLOPE	Item Slope	2.0		0.22

EIB01-Item 1 has 5 response items:

- 5-1=4 threshold parameters
- 1 item slop parameter

Item Slope:
Discrimination parameter, is a measure of how well an item can differentiate between individuals with different levels of the latent trait.

Threshold Parameter:
Difficulty parameters, are used in IRT models to indicate the point on the latent trait scale at which a respondent has a 50% chance of responding at or above a certain category. The parameters could be different in different IRT models

ADaM

- Should contain all individual items and summary scores (e.g., raw score, theta score, scale score (e.g., a standardized score such as T-score)) and associated standard errors.
- For CAT, additional information such as the number of items that were scored (i.e., scored count) and the number of items to which the patient responded (i.e., total item count) should be submitted to validate that the termination criteria for the CAT was met and that theta score was not calculated prematurely.

USUBJID	AVISIT	PARCAT1	PARAM	PARAMCD	AVAL	QSSEQ	VISIT	DTYPE	QSSTAT	QSREASND
A_100_1001	BASELINE	Example Item Bank v.1.0	EIB01-Item 1	EIB01	4	1	VISIT 1			
A_100_1001	BASELINE	Example Item Bank v.1.0	EIB03-Item 3	EIB03		2	VISIT 1		NOT DONE	RESPONSE NOT PROVIDED
A_100_1001	BASELINE	Example Item Bank v.1.0	EIB04-Item 4	EIB04	4	3	VISIT 1			
A_100_1001	BASELINE	Example Item Bank v.1.0	EIB05-Item 5	EIB05	5	4	VISIT 1			
A_100_1001	BASELINE	Example Item Bank v.1.0	EIB07-Item 7	EIB07	3	5	VISIT 1			
A_100_1001	BASELINE	Example Item Bank v.1.0	EIB-Raw Score	EIBRAW	12		VISIT 1			
A_100_1001	BASELINE	Example Item Bank v.1.0	EIB-Theta Score	EIBTHETA	2		VISIT 1			
A_100_1001	BASELINE	Example Item Bank v.1.0	EIB-T-Score	EIBTSCR	70		VISIT 1			
A_100_1001	BASELINE	Example Item Bank v.1.0	EIB-Standard Error	EIBSE	1.8		VISIT 1			
A_100_1001	VISIT 2	Example Item Bank v.1.0	All Questions	QSALL		6	VISIT 2		NOT DONE	STUDY SITE FAILED TO ADMINISTER
A_100_1001	VISIT 2	Example Item Bank v.1.0	EIB-Raw Score	EIBRAW			VISIT 2	PHANTOM		
A_100_1001	VISIT 2	Example Item Bank v.1.0	EIB-Theta Score	EIBTHETA			VISIT 2	PHANTOM		
A_100_1001	VISIT 2	Example Item Bank v.1.0	EIB-T-Score	EIBTSCR			VISIT 2	PHANTOM		
A_100_1001	VISIT 2	Example Item Bank v.1.0	EIB-Standard Error	EIBSE			VISIT 2	PHANTOM		
A_100_1001	VISIT 3	Example Item Bank v.1.0	EIB01-Item 1	EIB01	2	7	VISIT 3			
A_100_1001	VISIT 3	Example Item Bank v.1.0	EIB05-Item 5	EIB05	1	8	VISIT 3			
A_100_1001	VISIT 3	Example Item Bank v.1.0	EIB08-Item 8	EIB08	1	9	VISIT 3			
A_100_1001	VISIT 3	Example Item Bank v.1.0	EIB-Raw Score	EIBRAW	16		VISIT 3			
A_100_1001	VISIT 3	Example Item Bank v.1.0	EIB-Theta Score	EIBTHETA	2.5		VISIT 3			
A_100_1001	VISIT 3	Example Item Bank v.1.0	EIB-T-Score	EIBTSCR	75		VISIT 3			
A_100_1001	VISIT 3	Example Item Bank v.1.0	EIB-Standard Error	EIBSE	3.2		VISIT 3			

Thank You!